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COVID-19 vaccine boosters: what do we know so far?

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Why a booster dose?

The most effective regimen for Coronavirus Infectious Disease 19 (COVID-19) vaccination is still unknown as data keep evolving following the waning of immunity over time and the occurrence of new variants. Concerns about vaccine efficiency arose with the circulation of the Delta variant which has been associated with higher viral load and transmissibility (1). Indeed, several in vitro studies reported a modest decrease in the response of neutralising antibodies to the Delta variant for mRNA vaccines (2,3). Furthermore, observational studies reported a decrease in the BNT162b2 (Pfizer-BioNTech) vaccine's effectiveness against infection from more than 90% before the spread of the variant (4,5) to 42-80% after (6–8). Estimating vaccine effectiveness across studies and countries has been difficult since variants started circulating. Indeed, immunity due to vaccines and/or natural infection, population behaviour and public health policies vary tremendously and measures of effectiveness are impacted by these variations as well as by the waning of immunity over time. This decrease in immunity has been confirmed in several observational studies reporting a decrease in effectiveness against infection 5 to 6 months after the second dose, even though this decrease was less pronounced for hospitalisations or evolution to a severe form of the disease (9,10). Neutralising antibodies titres decreased over time for both mRNA vaccines and viral vector vaccines such as the Ad26.COV2-S vaccine (J&J/Janssen) (11–13). Other studies, on the contrary, observed that mediated-cell immunity was sustained 6 months after the second dose (13,14). Therefore, the question of a third dose or *booster* has recently been raised but still remains questionable.

Data supporting a booster dose

First, several concordant analyses showed that a third dose was useful in inducing a boost in humoral response for patients with immunosuppression or cancer who had no detectable antibodies or low antibodies titres (15,16), and among healthy participants (17).

Regarding real-life data, Israel has provided the most extensive data regarding COVID-19 vaccines as the country has one of the fastest growing vaccine coverage, with half of its population receiving at least one dose by late February 2021. In order to counter a potential waning in immunity, Israel decided to respond to the Delta wave with a booster program, allowing people above 60 years of age to receive a third dose. Following this decision, an observational study in Israel was conducted between the 30th of July and the 31st of August 2021, comparing the effectiveness of this third dose *versus* a two-dose regimen in this population (18). Administration of a third dose of the Pfizer/BioNTech vaccine with a three-week interval was associated with a significant reduction in confirmed infections and severe COVID-19 by a factor of 11.3 and 19.9, respectively (measured at least 12 days after the booster dose). The main limitations of this study are the potential unmeasured confounders such as previous COVID-19 infection or modifications in care-seeking behaviours. Moreover, follow-up was short and little is known about how long the reported increase in immunity provided by the booster dose will last or results regarding B and T cell responses on long-term protection.

Ethical issues of a booster dose and potential alternatives

Following these results, the Center for Disease Control and Prevention (United States of America) recommended in August 2021 a third dose for people aged 65 years and above and for those between 50 and 64 with underlying medical conditions. This was also recommended in France by the French National Authority for Health (Haute Autorité de Santé) for the same population on the 24th of August 2021. On the 6th of October, the French National Authority for Health recommended to extend the indication for a third dose to healthcare professionals. Nevertheless, booster administration raises ethical questions as most low- and middle-income countries are lacking vaccines for their population. By September 2021, only 3% of Africa's population was fully vaccinated according to the World Health Organization. As unvaccinated people are more likely to get infected and transmit the virus, spread of the SARS-CoV-2 in these countries contributes to the development of new variants that have the potential to be more transmissible or to better escape immunity. This was observed in China, where a preliminary analysis reported a lower secondary attack rate of Delta variants among vaccinated people *versus* unvaccinated or partially vaccinated individuals (19).

Therefore, searching for alternatives to a booster is a relevant question. The extension of the dose interval and heterologous vaccinations are also parameters under investigation to understand if it could increase the protection. A preliminary analysis observed an increase in humoral responses in participants who received a second dose 16 weeks after the first dose (*versus* 3 weeks) but mediated-cell immunity was not assessed (20). The Com-COV study showed that mixing ChAdOx1-S (Oxford/AstraZeneca) and Pfizer/BioNTech vaccines with a 28-day prime-boost interval was safe and induced a higher immune response than the standard homologous dosing regimens (21).

Conclusion

Administering a booster dose showed an improvement in humoral response, and real-life population data will soon be available for countries, which implemented this strategy in place. Nevertheless, making use of a booster is only an option for high-income countries and raises ethical questions. No global control of the pandemic is possible without equity in the supply of vaccines and leaving people unvaccinated across the world might currently be a more important threat than waning immunity.

Declarations of interest: none

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